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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/455,952	12/07/1999	GEORGE MICHALOPOULOS	A32516	5777

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EXAMINER

NAFF, DAVID M

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/45592

Applicant(s)

Khalopoulos et al

Examiner

N. C. P.

Group Art Unit

1857

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- ☒ Responsive to communication(s) filed on 12/20/02
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- ☒ Claim(s) 1-20 is/are pending in the application.
- Of the above claim(s) 8-11, 13 + 15-19 is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-7, 12, 14 + 20 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 - ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.
 - ☐ received in Application No. (Series Code/Serial Number) _____
 - ☐ received in this national stage application from the International Bureau (PCT Rule 1.7.2(a)).

*Certified copies not received: _____

Attachment(s)

- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413
- ☐ Notice of Reference(s) Cited, PTO-892
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Other _____

Office Action Summary

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/20/02 has been entered.

The amendment of 12/20/02 amended claims 1, 2 and 14, and added new claim 20.

Claims 8-11, 13 and 15-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7 (filed 7/19/01).

Claims examined on the merits are 1-7, 12, 14 and 20.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4-7, 12, 14 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitaka et al (Hepatology 1999) in view of Naughton et al (5,624,840) and Vacanti et al (5,759,830).

The claims are drawn to a method of generating a hepatic cell culture by co-culturing hepatocytes and nonparenchymal cells in the presence of growth factors and a matrix coated with at least one biologically active molecule that promotes cell adhesion, proliferation or survival under conditions sufficient to allow for the proliferation of

the hepatocytes while retaining hepatic function of the hepatocytes. Also claimed (claims 14 and 20) is a population of hepatocytes and nonparenchymal cells associated with a coated matrix as required in the process.

5 Mitaka et al disclose obtaining hepatic cells and nonparenchymal cells from liver tissue and culturing the hepatic cells and nonparenchymal cells together for hepatic organoid reconstruction.

Naughton et al disclose growing stromal cells on a three-dimensional matrix such as made from nylon or polystyrene (col 8, line 1) which may
10 be coated with collagen (col 8, line 8) to form a three-dimensional stromal matrix (col 8, lines 30-40), and then growing hepatocytes on the stromal matrix to form tissue having liver function (col 11, lines 54-57).

Vacanti et al disclose growing hepatocytes (col 6, line 28) in a
15 three-dimensional fibrous scaffold to form tissue having liver function for implanting (col 5, line 35 to col 6, line 62, and col 12, lines 17-47). The fibers of the scaffold may be coated with collagen to enhance cell attachment (col 10, lines 44-47), and epithelial cells may be attached to the scaffold in combination with the hepatocytes (col 12,
20 lines 25-27).

It would have been obvious to carry out the culturing of hepatic cells and nonparenchymal cells together as disclosed by Mitaka et al on a three-dimensional matrix or scaffold as suggested by Naughton et al and Vacanti et al to obtain the function of the matrix or scaffold in
25 producing tissue having liver function. The claims do not exclude the

matrix containing stromal tissue as disclosed by Naughton et al.
Moreover, it would have been obvious to grow hepatocytes directly on the
matrix without first forming stromal tissue when the function of stromal
tissue is not needed, and since it is clear from Vacanti et al that
5 stromal tissue can be omitted.

Response to Arguments

Applicant's arguments filed 12/20/02 have been fully considered but
they are not persuasive.

A 131 Declaration by Michalopoulos et al has been submitted to
10 antedate Mitaka et al. However, the declaration fails to state that the
invention was conceived and reduced to practice in this country.
Additionally, the present claims are not commensurate in scope with the
invention carrier out as shown by the exhibits of the declaration. In
particular, hepatocytes containing a small amount of non-parenchymal
15 cells were obtained from liver tissue and were grown on beads in a roller
bottle using a medium containing HGF and EGF.

Claim Rejections - 35 USC § 103

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable
over the references as applied to claims 1, 2, 4-7, 12, 14 and 20 above,
20 and further in view of Matsui et al (5,298,615).

The claim requires the matrix to be in the form of polystyrene
beads.

Matsui et al disclose that it is standard procedure to culture
animal cells on microcarriers such as polystyrene beads coated with
25 collagen (col 2, lines 10-25).

When using a matrix or scaffold as suggested by Naughton et al and Vacanti et al to culture the cells of Mitaka et al as set forth above, it would have been obvious to provide the matrix or scaffold in the form of polystyrene beads coated with collagen as suggested Matsui et al
5 disclosing the use of such beads as being a standard technique for culturing animal cells.

Response to Arguments

Comments set forth above in response to arguments also apply to this rejection.

10 Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is (703) 308-0520. The examiner can normally be reached on Monday-Thursday and every other Friday from about 8:30 AM to about 6:00 PM.


15 If attempts to reach the examiner by telephone are unsuccessful, a message can be left on voice mail.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn, can be reached at telephone number (703) 308-4743.

20 The fax phone number is (703) 872-9306 before final rejection or (703) 872-9307 after final rejection.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

25 DMN
3/24/02


DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 12857